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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 344184D19973	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 02/05698	International filing date *(day/month/year)* 06.12.2002	Priority date *(day/month/year)* 06.12.2001
International Patent Classification (IPC) or both national classification and IPC A61K48/00		
Applicant INSTITUT NATIONAL DE LA SANTE ET DE LA ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the International application
   VIII ☐ Certain observations on the International application

Date of submission of the demand	Date of completion of this report
04.07.2003	15.01.2004
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ludwig, G Telephone No. +49 89 2399-8698

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/05698

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-60 as originally filed

Claims, Numbers

1-20 received on 04.11.2003 with letter of 03.11.2003

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

D1: **US 2001/038836** A1 (LEONE PAOLA ET AL) 8 November 2001 (2001-11-08)

D2: **FR-A-2 729 399** (INST NAT SANTE RECH MED) 19 July 1996 (1996-07-19)

D3: **DATABASE BIOSIS** [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2001 ROGELIUS N ET AL: 'Hematopoietic stem cells populate the brain after intravenous injection into irradiated mice.' **Database accession no. PREV200100486592** XP002238249 & SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 57 31st Annual Meeting of the Society for Neuroscience;San Diego, California, USA; November 10-15, 2001 ISSN: 0190-5295

cf. the citations indicated in the International search report

ITEM V:

1. Document D1 discloses the use of **human** CD34+ stem cells of myeloid origin recombinantly transformed/transfected with the KDR gene (kinase tyrosine receptor) for delivery of these cells to the brain by **intraveneous** injection (intraveneous injection: page 7, paragraph 88, line 13 and the whole paragraph; human CD34+ cells: page 4, paragraph 41, page 5, paragraph 51, lines 5-9, page 4, paragraph 47, last two lines).

   The method is indicated to be generally applicable for CNS disorders, as for instance ***Alzheimer***, by using the appropriate genes needed for these diseases (page 1, paragraph 3 and line 7 of this paragraph).

   In the examples stereotactical intracranial surgery was used for application of the KDR+ cells into *mice*, i.e. by direct infusion of KDR+ cells into their lateral ventricle/hippocampus (page 6, paragraphs 63 and 66).

   Document D3 discloses that **intraveneous** injection of GFP-transduced *mouse* hematopoietic stem cells into mice leads to population of the mouse brain by GFP-transduced cells with **microglial** morpholgy.
   Hence D3 indicates that genetically transformed hematopoietic stem cells can

populate the brain after intraveneous injection and turn into microglial cells.

Document D2 discloses transformation of CD34+ hematopoietic cells by the ADN gene to correct adrenoleucodystrophy, a CNS disease in which there is progressive demyelinisation of the central nervous system (page 6, last paragraph), and application of these cells by implantation (page 6, paragraph 2 from the bottom).

2. The applicant has shown in the mouse NOD-SCID model that **intraveneously** injected recombinant **human** CD34+ cells can migrate into the mouse brain and differentiate into human *microglia*, while expressing the recombinant therapeutic protein for several months when administrated .

3. The problem to be solved by the application is to treat CNS (=central nervous system) diseases.

The problem is solved according to claim 1 of the invention by **intraveneous** administration of **human** CD34+ cells which comprise the nucleic acid of interest for this CNS disorder.

Claim 1 is not however not novel vis-a-vis document D1 as characterized above. The rest of the claims also appear to lack novelty/inventive step in view of this document.

4. If document D3 is considered as closest state of the art document, a combination of this document with document D1 would be considered to lead to the invention as disclosed in the application.

The claims are therefore not considered as inventive in view of document D3 when combined with document D1.

CLAIMS

1. Use of a nucleic acid of interest for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or susceptible to being affected by a CNS disorder, wherein said composition is a composition enriched in human cells expressing the CD34 marker or human cells capable of giving rise to cells expressing the CD34 marker, at least of portion of said cells comprising a nucleic acid of interest, and wherein at least a portion of said administered cells are capable of migrating to the CNS and expressing the nucleic acid of interest in the CNS of this subject.

2. Use according to claim 1, wherein said administered cells are capable of giving rise to microglia in the CNS of a mammal.

3. Use of a nucleic acid sequence encoding a polypeptide of interest for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or susceptible to being affected by a CNS disorder under conditions that result in the expression of a polypeptide of interest at a level that provides a therapeutic effect in said subject, wherein said composition is a composition comprising hematopoietic progenitor cells or hematopoietic stem cells isolated from cells comprising hematopoietic progenitor or hematopoietic stem cells obtained from a human subject, and wherein a nucleic acid encoding a polypeptide of interest has been introduced to said isolated hematopoietic progenitor or stem cell.

4. Use of cells for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or susceptible to being affected by a CNS disorder, wherein said composition is a composition enriched in human cells expressing the CD34 marker or human cells capable of giving rise to cells expressing the CD34 marker, and wherein at least a portion of said administered cells are capable of migrating to the CNS and giving rise to microglia.

5. Use according to one of claims 1 to 4, wherein said administration results in a reduction in the severity of central nervous system damage or symptoms of a central nervous system disorder.

6. Use of a nucleic acid of interest for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or

CLAIMS

1. Use of a nucleic acid of interest for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or susceptible to being affected by a CNS disorder, wherein said composition is a composition enriched in human cells expressing the CD34 marker or human cells capable of giving rise to cells expressing the CD34 marker, at least of portion of said cells comprising a nucleic acid of interest, and wherein at least a portion of said administered cells are capable of migrating to the CNS and expressing the nucleic acid of interest in the CNS of this subject.

2. Use according to claim 1, wherein said administered cells are capable of giving rise to microglia in the CNS of a mammal.

3. Use of a nucleic acid sequence encoding a polypeptide of interest for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or susceptible to being affected by a CNS disorder under conditions that result in the expression of a polypeptide of interest at a level that provides a therapeutic effect in said subject, wherein said composition is a composition comprising hematopoietic progenitor cells or hematopoietic stem cells isolated from cells comprising hematopoietic progenitor or hematopoietic stem cells obtained from a human subject, and wherein a nucleic acid encoding a polypeptide of interest has been introduced to said isolated hematopoietic progenitor or stem cell.

4. Use of cells for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or susceptible to being affected by a CNS disorder, wherein said composition is a composition enriched in human cells expressing the CD34 marker or human cells capable of giving rise to cells expressing the CD34 marker, and wherein at least a portion of said administered cells are capable of migrating to the CNS and giving rise to microglia.

5. Use according to one of claims 1 to 4, wherein said administration results in a reduction in the severity of central nervous system damage or symptoms of a central nervous system disorder.

6. Use of a nucleic acid of interest for the manufacture of a composition for intraveinous administration to a human, for the treatment of a subject affected by or

susceptible to being affected by a CNS disorder under conditions that result in the expression of a polypeptide of interest at a level that provides a therapeutic effect in said subject, wherein said composition is a composition enriched in human cells expressing the CD34 marker or human cells capable of giving rise to cells expressing the CD34 marker, at least of portion of said cells being recombinant cells comprising a nucleotide sequence encoding said polypeptide operably linked to expression control elements.

7. Use according to claim 6, wherein at least a portion of said administered cells migrate to the CNS, give rise to microglia and express the nucleic acid of interest in the CNS of said subject.

8. Use according to one of claims 1 to 7, wherein said administered cells expressing the CD34 marker, said cells capable of giving rise to cells expressing the CD34 marker, or said hematopoietic progenitor or hematopoietic stem cells differentiate into a microglia cell.

9. Use according to one of claims 3 and 6, wherein at least a portion of said administered cells express the nucleic acid of interest in the CNS of said subject.

10. Use according to one of claims 1, 4 and 6, wherein at least 20 % of cells in said cell composition express the CD34+ marker.

11. Use according to one of claims 1, 4 and 6, wherein the subject to be treated is pretreated in order to enhance engraftment of said cells expressing the CD34 marker, cells capable of giving rise to cells expressing the CD34 marker, hematopoietic progenitor or stem cells.

12. Use according to one of claims 1, 4 and 6, wherein said cells expressing the CD34+ marker, cells capable of giving rise to cells expressing the CD34 marker, hematopoietic progenitor cells or hematopoietic stem cells are prior isolated.

13. Use according to claim 4, wherein said cells expressing the CD34 marker or cells capable of giving rise to cells expressing the CD34 marker are recombinant cells comprising a nucleic acid of interest.

14. Use according to one of claims 1, 3, 4 and 6, wherein at least a portion of said cells expressing the CD34+ marker, cells capable of giving rise to cells expressing the CD34 marker, hematopoietic progenitor cells or hematopoietic stem cells are transduced with a vector comprising a nucleic acid of interest operably linked to a promotor capable of effecting the expression of said nucleic acid of interest in said cells.

15. Use according to one of claims 1, 3, 4 and 6, wherein at least a portion of said cells expressing the CD34+ marker, cells capable of giving rise to cells expressing the CD34 marker, hematopoietic progenitor cells or hematopoietic stem cells are transduced with a viral vector, preferably with a lentiviral vector.

16. Use according to claim 3, wherein said hematopoietic progenitor or hematopoietic stem cells express the CD34+ marker or are capable of differentiating into cells expressing the CD34+ marker.

17. Use according to one of claims 1, 4 and 6, wherein said cells expressing the CD34+ marker or cells capable of giving rise to cells expressing the CD34 marker are hematopoietic progenitor cells or hematopoietic stem cells.

18. Use according to one of claims 1, 3, 6 and 13, wherein said nucleic acid encodes a non-secreted or a secreted protein.

19. Use according to one of claims 1 to 18, wherein the CNS disorder which affects or which is susceptible to affect the subject is characterized by diffuse neurodegeneration, preferably the Alzheimer's disease.

20. Use according to one of claims 1 to 19, wherein the administered cells are autologous to the subject to be treated.